

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name Jeffrey Russel Examiner # 62785 Date: 6-19-2003
 An Unit 1654 Phone Number 308-3975 Serial Number 09/830,741
 Mail Box and Bldg Room Location _____ Results Format Preferred (circle) PAPER DISK E-MAIL
CM1-11D13/CM1-7807

If more than one search is submitted, please prioritize searches in order of need.

 Please provide a detailed statement of the search topic and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

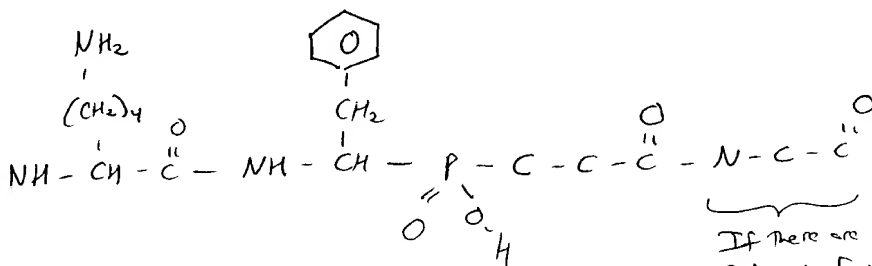
Title of Invention: Phosphatase peptide analogs for the treatment of fibrotic disorders

Inventors (please provide full names): E. Burchardt, M. Schauer, W. Stocker, T. Lampe

Earliest Priority Filing Date 4-30-2001

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please search the following partial structure:



If there are many hits on the first part of the structure, please add this residue.

If necessary please use the keywords fibro?, pcp, procollagen, laminin, collagen.

Thank you.
 JSR

=> d que

L1 STR

15
NH2

CH2 14 22
C
CH2 13 19 C C 23

CH2 12 C C 21
18 C

CH2 11 CH2 20

3 6
N C C N C P C C C O
1 2 4 5 7 8 9 10
O O O
16 24 25

NODE ATTRIBUTES:

CONNECT IS E3 RC AT 2
CONNECT IS E2 RC AT 4
CONNECT IS E3 RC AT 5
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE

L3 33 SEA FILE=REGISTRY SSS FUL L1
L4 8 SEA FILE=HCAPLUS ABB=ON PLU=ON L3
L5 3 SEA FILE=HCAPLUS ABB=ON PLU=ON L4 AND (FIBRO? OR PCP OR
PROCOLLAGEN OR LAMININ OR COLLAGEN)
L6 8 SEA FILE=HCAPLUS ABB=ON PLU=ON L4 OR L5

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L6 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:76639 HCAPLUS

DOCUMENT NUMBER: 138:131168

TITLE: Phosphinate-peptide analogues as inhibitors of
procollagen C-proteinase (**pcp**) for
treating **fibrotic** diseases

INVENTOR(S): Burchardt, Elmar Reinhold; Stocker, Walter
PATENT ASSIGNEE(S): Germany

SOURCE: PCT Int. Appl., 26 pp.

CODEN: PIXXD2

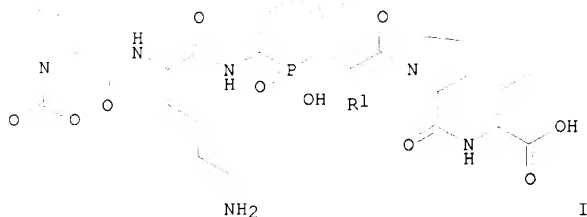
DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003007980	A1	20030130	WO 2002-DE2583	20020713
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10134243	A1	20030327	DE 2001-10134243	20010714
PRIORITY APPLN. INFO.:			DE 2001-10134243 A	20010714
GI				



AB The invention discloses the use of phosphinate-peptide analogs I (R1 = H, Me) as inhibitors of **procollagen** C-proteinase, for treating **fibrotic** diseases.

IT **489412-73-9 489412-73-9D**, stereoisomers

489412-74-0 489412-74-0D, stereoisomers

489412-75-1 489412-75-1D, stereoisomers

489412-76-2 489412-76-2D, stereoisomers

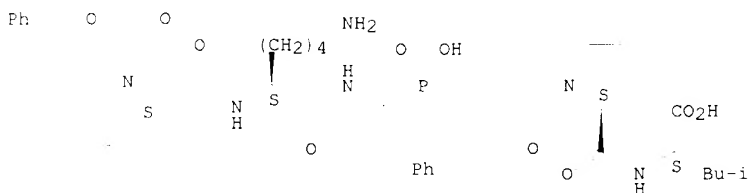
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(phosphinate-peptide analogs as inhibitors of **procollagen** C-proteinase (**pcp**) for treating **fibrotic** diseases)

RN **489412-73-9 HCAPLUS**

CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysylphenylalanyl-.psi.(PO(OH)-CH2)-glycyl-L-prolyl- (9CI) (CA INDEX NAME)

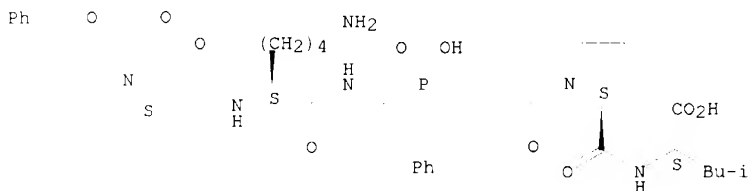
Absolute stereochemistry.



RN 489412-73-9 HCAPLUS

CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysylphenylalanyl-.psi.(PO(OH)-CH2)-glycyl-L-prolyl- (9CI) (CA INDEX NAME)

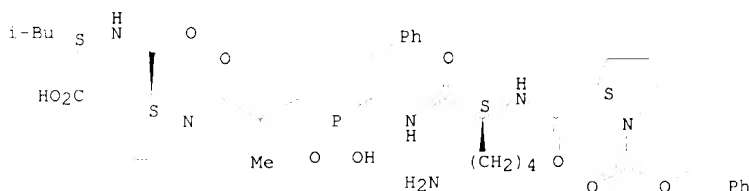
Absolute stereochemistry.



RN 489412-74-0 HCAPLUS

CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysylphenylalanyl-.psi.(PO(OH)-CH2)-alanyl-L-prolyl- (9CI) (CA INDEX NAME)

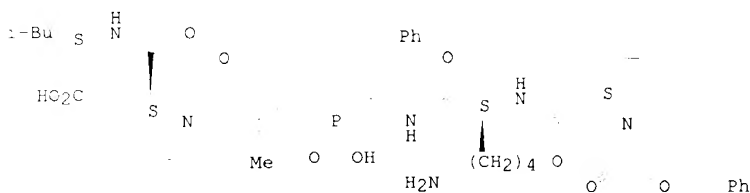
Absolute stereochemistry.



RN 489412-74-0 HCAPLUS

CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysylphenylalanyl-.psi.(PO(OH)-CH2)-alanyl-L-prolyl- (9CI) (CA INDEX NAME)

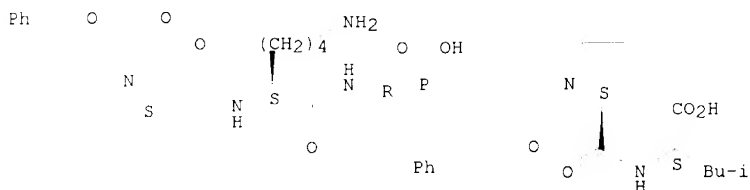
Absolute stereochemistry.



RN 489412-75-1 HCAPLUS

CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-L-phenylalanyl-.psi.(PO(OH)-CH2)-glycyl-L-prolyl- (9CI) (CA INDEX NAME)

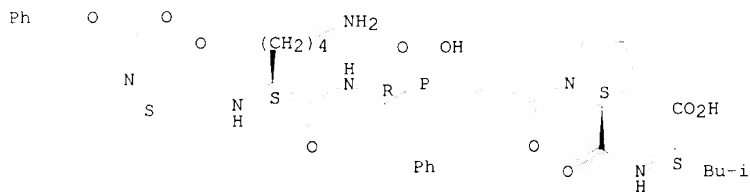
Absolute stereochemistry.



RN 489412-75-1 HCAPLUS

CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-L-phenylalanyl-.psi.(PO(OH)-CH2)-glycyl-L-prolyl- (9CI) (CA INDEX NAME)

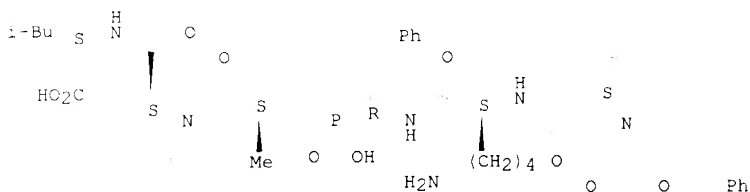
Absolute stereochemistry.



RN 489412-76-2 HCAPLUS

CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-L-phenylalanyl-.psi.(PO(OH)-CH2)-L-alanyl-L-prolyl- (9CI) (CA INDEX NAME)

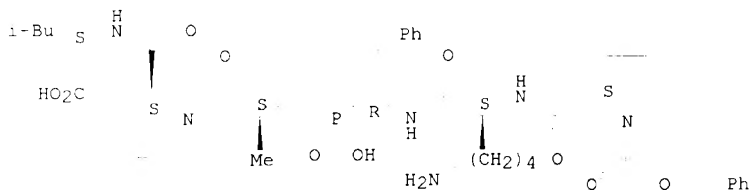
Absolute stereochemistry.



RN 489412-76-2 HCAPLUS

CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-L-phenylalanyl-
.psi.(PO(OH)-CH2)-L-alanyl-L-prolyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:289131 HCAPLUS

DOCUMENT NUMBER: 132:303510

TITLE: Phosphinate peptide analogs for the treatment of
fibrotic diseaseINVENTOR(S): Burchardt, Elmar-Reinhold; Schauer, Michael; Stocker,
Walter

PATENT ASSIGNEE(S): Bayer A.-G., Germany

SOURCE: Ger. Offen., 12 pp.

CODEN: GWXXBX

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

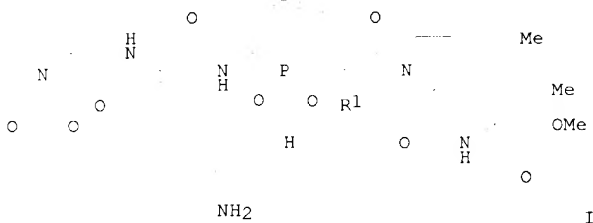
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19850072	A1	20000504	DE 1998-19850072	19981030
WO 2000027377	A2	20000518	WO 1999-EP8181	19991028
WO 2000027377	A3	20001116		

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CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,
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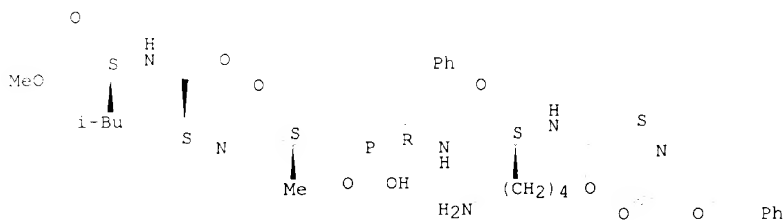
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 CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
 EP 1124845 A2 20010822 EP 1999-969897 19991028
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 IE, SI, LT, LV, FI, RO
 JP 2002529403 T2 20020910 JP 2000-580606 19991028
 PRIORITY APPLN. INFO.: DE 1998-19850072 A 19981030
 WO 1999-EP8181 W 19991028

GI



- AB Phosphinate peptide analogs I (R1 = H, Me) are disclosed as inhibitors of **procollagen** C proteinase for the treatment of **fibrotic** disease, e.g. liver **fibrosis**.
- IT 209247-63-2 209247-63-2D, stereoisomers
 209247-69-8 209247-69-8D, stereoisomers
 265979-02-0 265979-02-0D, stereoisomers
 265979-03-1 265979-03-1D, stereoisomers
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (phosphinate peptide analogs for the treatment of **fibrotic** disease)
- RN 209247-63-2 HCAPLUS
- CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-(2S)-3-[[{(1R)-1-amino-2-phenylethyl]hydroxyphosphinyl]-2-methylpropanoyl-L-prolyl-, methyl ester (9CI) (CA INDEX NAME)

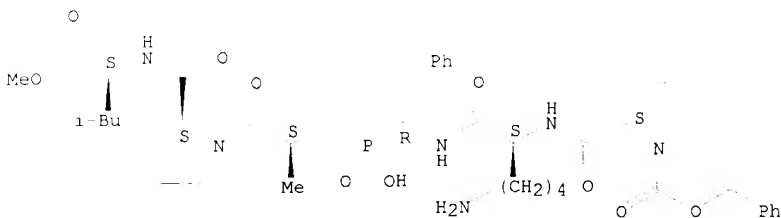
Absolute stereochemistry.



RN 209247-63-2 HCAPLUS

CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-(2S)-3-[[[(1R)-1-amino-2-phenylethyl]hydroxyphosphinyl]-2-methylpropanoyl-L-prolyl-, methyl ester (9CI) (CA INDEX NAME)

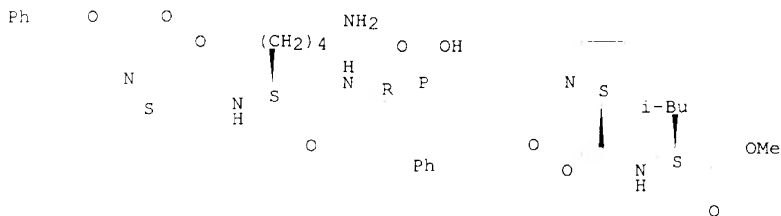
Absolute stereochemistry.



RN 209247-69-8 HCAPLUS

CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-3-[[[(1R)-1-amino-2-phenylethyl]hydroxyphosphinyl]propanoyl-L-prolyl-, methyl ester (9CI) (CA INDEX NAME)

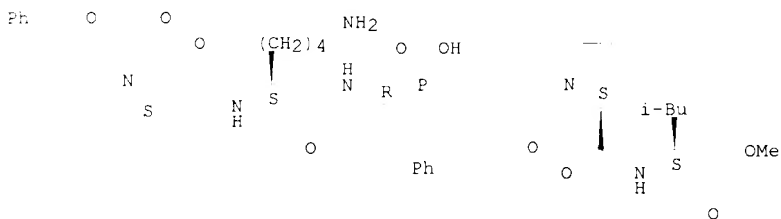
Absolute stereochemistry.



RN 209247-69-8 HCAPLUS

CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-3-[[[(1R)-1-amino-2-phenylethyl]hydroxyphosphinyl]propanoyl-L-prolyl-, methyl ester (9CI) (CA INDEX NAME)

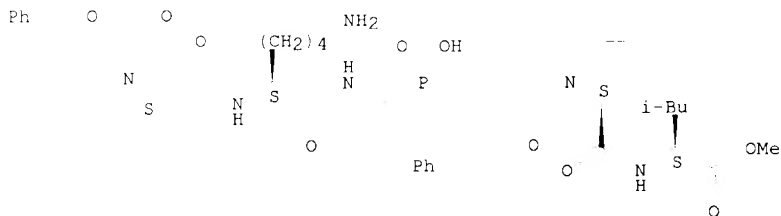
Absolute stereochemistry.



RN 265979-02-0 HCAPLUS

CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-3-[(1-amino-2-phenylethyl)hydroxyphosphinyl]propanoyl-L-prolyl-, methyl ester (9CI) (CA INDEX NAME)

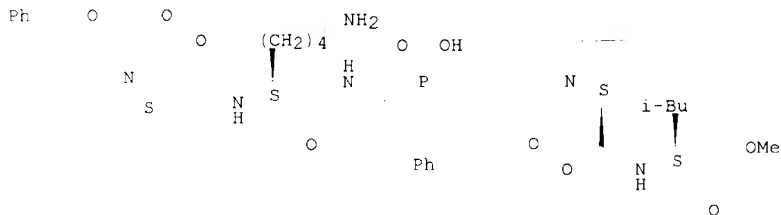
Absolute stereochemistry.



RN 265979-02-0 HCAPLUS

CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-3-[(1-amino-2-phenylethyl)hydroxyphosphinyl]propanoyl-L-prolyl-, methyl ester (9CI) (CA INDEX NAME)

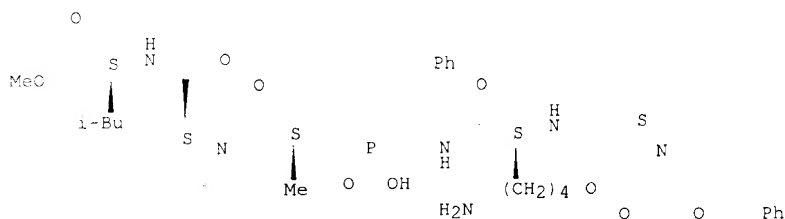
Absolute stereochemistry.



RN 265979-03-1 HCAPLUS

CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-(2S)-3-[(1-amino-2-phenylethyl)hydroxyphosphinyl]-2-methylpropanoyl-L-prolyl-, methyl ester (9CI) (CA INDEX NAME)

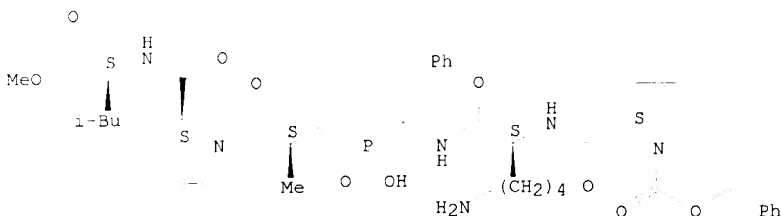
Absolute stereochemistry.



RN 265979-03-1 HCAPLUS

CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-(2S)-3-[(1-amino-2-phenylethyl)hydroxyphosphinyl]-2-methylpropanoyl-L-prolyl-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:289115 HCAPLUS

DOCUMENT NUMBER: 129:78349

TITLE: Phosphinic peptides, the first potent inhibitors of astacin, behave as extremely slow-binding inhibitors

AUTHOR(S): Yiallourous, Irene; Vassiliou, Stamatia; Yiotakis, Athanasios; Zwilling, Robert; Stocker, Walter; Dive, Vincent

CORPORATE SOURCE: Zoologisches Institut der Universität Heidelberg, Physiologie, Heidelberg, D-69120, Germany

SOURCE: Biochemical Journal (1998), 331(2), 375-379
CODEN: BIJOAK; ISSN: 0264-6021

PUBLISHER: Portland Press Ltd.

DOCUMENT TYPE: Journal

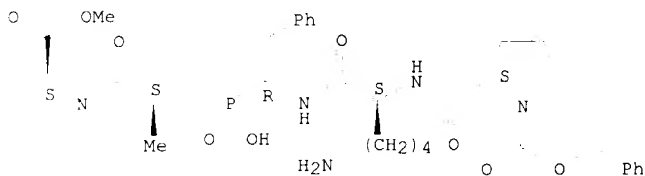
LANGUAGE: English

AB A series of phosphinic pseudo-peptides varying in length and compn. have been designed as inhibitors of the crayfish zinc endopeptidase astacin, the prototype of the astacin family and of the metzincin superfamily of metalloproteinases. The most efficient phosphinic peptide, fluorenylmethyloxycarbonyl-Pro-Lys-Phe.psi.(PO2CH2)Ala-Pro-Leu-Val, binds to astacin with a K_i value of 42 nM, which is about three orders of magnitude below the corresponding values for previously used hydroxamic acid derivs. However, the rate consts. for assocn. ($k_{on} = 96.8 \text{ M}^{-1} \text{ s}^{-1}$) and dissocn. ($k_{off} = 4.1 \text{ times } 10^{-6} \text{ s}^{-1}$) are evidence for the extremely slow binding behavior of this compd. N-terminally or C-terminally

truncated phosphinic analogs of this parent mol. are much less potent, indicating a crit. role of the peptide size on the potency. In particular, omission of the N-terminal proline residue leads to a 40-fold increase in K_i which is mostly due to a 75-fold higher k_{off} value. These findings are consistent with the previously solved crystal structure of astacin complexed with one of the phosphinic peptides, benzyloxycarbonyl-Pro-Lys-Phe.psi.(PO₂CH₂)Ala-Pro-O-Me, $K_i = 14 \mu\text{M}$ [Grams, Dive, Yiotakis, Yiallourous, Vassiliou, Zwilling, Bode and Stocker (1996) Nature Struct. Biol. 3, 671-675]. This structure also reveals that the phosphinic group binds to the active site as a transition-state analog. The extremely slow binding behavior of the phosphinic peptides is discussed in the light of the conformational changes involving a unique tyrosine switch in the structure of astacin upon inhibitor binding. The phosphinic peptides may provide a rational basis for the design of drugs directed toward other members of the astacin family which, like bone morphogenetic protein 1 (BMP1; i.e. the **procollagen** C-proteinase), have become targets of pharmacol. research.

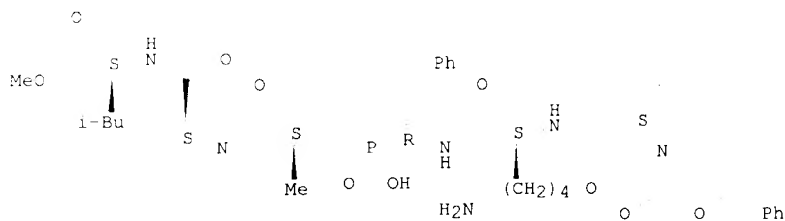
IT 209247-62-1 209247-63-2 209247-64-3
209247-65-4 209247-68-7 209247-69-8
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(phosphinic peptides, the first potent inhibitors of astacin, behave as extremely slow-binding inhibitors)
RN 209247-62-1 HCAPLUS
CN L-Proline, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-(2S)-3-[[[(1R)-1-amino-2-phenylethyl]hydroxyphosphinyl]-2-methylpropanoyl-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 209247-63-2 HCAPLUS
CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-(2S)-3-[[[(1R)-1-amino-2-phenylethyl]hydroxyphosphinyl]-2-methylpropanoyl-L-prolyl-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

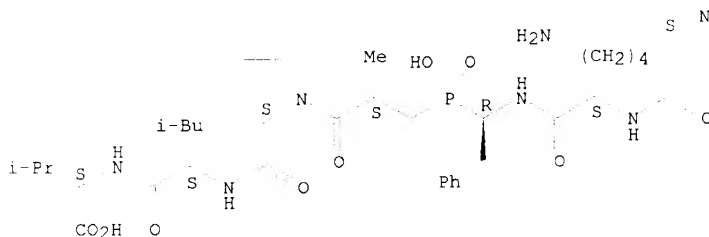


RN 209247-64-3 HCAPLUS

CN L-Valine, 1-[(9H-fluoren-9-ylmethoxy)carbonyl]-L-prolyl-L-lysyl-(2S)-3-
 [[(1R)-1-amino-2-phenylethyl]hydroxyphosphinyl]-2-methylpropanoyl-L-prolyl-
 L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

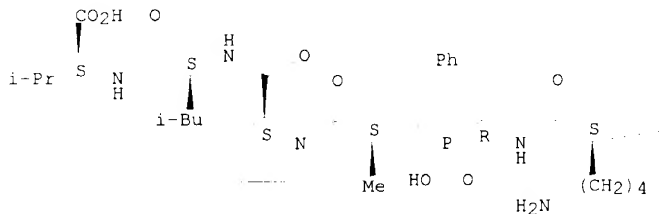
RN 209247-65-4 HCAPLUS

CN L-Valine, N2-[(9H-fluoren-9-ylmethoxy)carbonyl]-L-lysyl-(2S)-3-[[[(1R)-1-
 amino-2-phenylethyl]hydroxyphosphinyl]-2-methylpropanoyl-L-prolyl-L-leucyl-

(9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



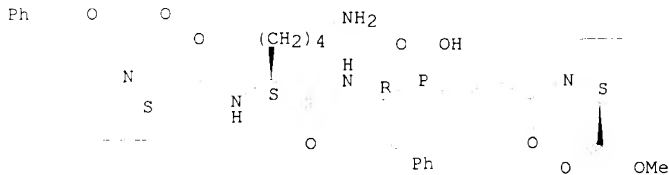
PAGE 1-B



RN 209247-68-7 HCAPLUS

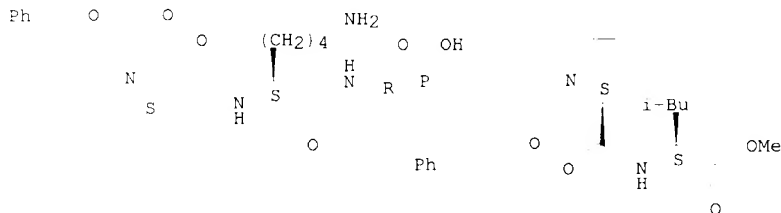
CN L-Proline, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-3-[[(1R)-1-amino-2-phenylethyl]hydroxyphosphinyl]propanoyl-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 209247-69-8 HCAPLUS
 CN L-Leucine, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-3-[[[(1R)-1-amino-2-phenylethyl]hydroxyphosphinyl]propanoyl-L-prolyl-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:531753 HCAPLUS

DOCUMENT NUMBER: 125:248435

TITLE: Protection of the Hydroxyphosphinyl Function of Phosphinic Dipeptides by Adamantyl. Application to the Solid-Phase Synthesis of Phosphinic Peptides

AUTHOR(S): Yiotakis, Athanasios; Vassiliou, Stamatia; Jiracek, Jiri; Dive, Vincent

CORPORATE SOURCE: Department of Organic Chemistry, University of Athens, Athens, 15771, Greece

SOURCE: Journal of Organic Chemistry (1996), 61(19), 6601-6605
 CODEN: JOCEAH; ISSN: 0022-3263

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To develop solid-phase synthesis of phosphinic peptides, different FmocXaa.PSI.[PO(OAd)CH₂]XaaOH [Fmoc = (fluorenylmethoxy)carbonyl, Ad = 1-adamantyl] building blocks have been prepd. In this respect, the protection of the hydroxyphosphinyl function in these phosphinic dipeptides by the adamantyl group turns out to be convenient. The phosphinic adamantyl esters are completely stable under basic conditions and can be removed under relatively mild acidic conditions. Using these building blocks, despite the bulkiness of the adamantyl group, no particular problem of coupling was obsd. during the solid-phase synthesis of phosphinic peptides by the Fmoc strategy. The developed methodol. is of particular interest to facilitate the development of potent inhibitors of zinc-metallo proteases.

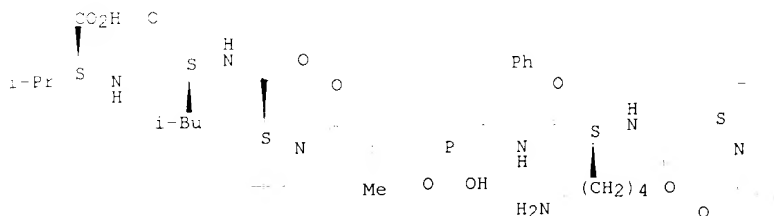
IT 182193-50-6P

RL: SPN (Synthetic preparation); PREP (Preparation)
 (solid-phase synthesis of phosphinic peptides)

RN 182193-50-6 HCAPLUS

CN L-Valine, N-[N-[1-[3-[hydroxy(2-phenyl-1-[[[N2-[1-[(phenylmethoxy)carbonyl]-L-prolyl]-L-lysyl]amino]ethyl]phosphinyl]-2-methyl-1-oxopropyl]-L-prolyl]-L-leucyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B

O Ph

AB A new systematic approach, based on combinatorial chem. of phosphinic peptides, is proposed for rapid development of highly potent and selective inhibitors of zinc metalloproteases. This strategy first evaluates the effects on the inhibitory potency and selectivity of the following parameters: (1) size of the phosphinic peptides, (2) position of the phosphinic bond in the sequence, and (3) the state (free or blocked) of the peptide extremities. After this selection step, the influence of the

inhibitor sequence is analyzed to det. the identity of the residues that optimized both the potency and the selectivity. We demonstrate the efficiency of this novel approach in rapid identification of the first potent inhibitor of the mammalian zinc endopeptidase neurolysin (24-16), able to discriminate between this enzyme and the related zinc endopeptidase thimet oligopeptidase (24-15). The most potent and selective inhibitor developed in this study, Pro-LPhe.psi.(PO2CH2)Gly-Pro, displays a K_i value of 4 nM for 24-16 and is 2000 times less potent on 24-15. The specific recognition of such a free phosphinic tetrapeptide by 24-16, as well as the unique specificity of the 24-16 S2 and S2' subsites for proline, unveiled by this study, are discussed in terms of their possible significance for the function of this enzyme and its related zinc endopeptidase activities.

IT 181111-15-9 181111-35-3 181111-55-7
181111-75-1

RI: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(development of the first potent and selective inhibitor of the zinc endopeptidase neurolysin using a systematic approach based on combinatorial chem. of phosphinic peptides)

RN 181111-15-9 HCAPLUS

CN Propanoic acid, 3-[[1-[(2,6-diamino-1-oxohexyl)amino]-2-phenylethyl]hydroxyphosphinyl]- (9CI) (CA INDEX NAME)

O

HO2C CH2 CH2 P OH O NH2

Ph CH2 CH-NH- C-CH- (CH2)4- NH2

RN 181111-35-3 HCAPLUS

CN Propanoic acid, 3-[[1-[(2-(acetyl amino)-6-amino-1-oxohexyl)amino]-2-phenylethyl]hydroxyphosphinyl]- (9CI) (CA INDEX NAME)

O

HO2C CH2 CH2 P OH O NHAc

Ph CH2 CH-NH- C-CH- (CH2)4- NH2

RN 181111-55-7 HCAPLUS

CN Phosphinic acid, (3-amino-3-oxopropyl)[1-[(2,6-diamino-1-oxohexyl)amino]-2-phenylethyl]- (9CI) (CA INDEX NAME)

O

O

H2N C CH2-CH2- P OH O NH2

Ph CH2 CH-NH- C-CH- (CH2)4- NH2

RN 181111-75-1 HCAPLUS

CN Phosphinic acid, [1-[[2-(acetlamino)-6-amino-1-oxohexyl]amino]-2-phenylethyl](3-amino-3-oxopropyl)- (9CI) (CA INDEX NAME)

O O

H₂N C CH₂ CH₂ P OH O NHAc

Ph CH₂ CH NH C CH (CH₂)₄ NH₂

L6 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:481069 HCAPLUS

DOCUMENT NUMBER: 125:161938

TITLE: Structure of astacin with a transition-state analog inhibitor

AUTHOR(S): Grams, Frank; Dive, Vincent; Yiotakis, Athanasios; Yiallourous, Irene; Vassiliou, Stamatia; Zwilling, Robert; Bode, Wolfram; Stoecker, Walter

CORPORATE SOURCE: Max-Planck-Inst. Biochem., Planegg-Martinsried, D-82152, Germany

SOURCE: Nature Structural Biology (1996), 3(8), 671-675

CODEN: NSBIEW; ISSN: 1072-8368

PUBLISHER: Nature Publishing Co.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The structure of the zinc peptidase astacin in complex with a phosphinic peptide suggests that a special role is played by the side chain of a zinc-bound tyrosine, which is shifted to form a hydrogen bond to the phosphinyl group-a mimic of the carboxyanion of the transition state.

IT 180156-46-1

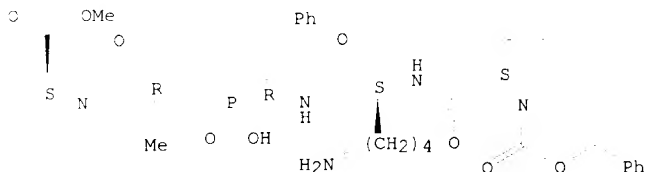
RL: PRP (Properties)

(complexes with astacin; structure of astacin with a transition-state analog inhibitor)

RN 180156-46-1 HCAPLUS

CN L-Proline, 1-[(phenylmethoxy)carbonyl]-L-prolyl-L-lysyl-(2R)-3-[[[(1R)-1-amino-2-phenylethyl]hydroxyphosphinyl]-2-methylpropanoyl-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



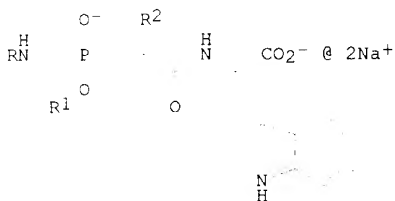
L6 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:368760 HCAPLUS

DOCUMENT NUMBER: 125:168620

TITLE: Highly potent and selective inhibitors of endothelin

converting enzyme
 AUTHOR(S): Chackalamannil, Samuel; Chung, Shin; Stamford, Andrew
 W.; McKittrick, Brian A.; Wang, Yuguang; Tsai,
 Hsingan; Cleven, Renee; Fawzi, Ahmad; Czarniecki,
 Michael
 CORPORATE SOURCE: Schering-Plough Res. Inst., Kenilworth, NJ, 07033, USA
 SOURCE: Bioorganic & Medicinal Chemistry Letters (1996),
 6(11), 1257-1260
 CODEN: BMCLE8; ISSN: 0960-894X
 PUBLISHER: Elsevier
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



AB Phosphinic acid derivs. I [R = H, Z, Z-L-Leu, MeSO2-L-Lys, MeSO2-L-Lys(Z);
 R1 = 2-naphthylmethyl, PhCH2, Me2CHCH2; R2 = Me, CHMe2, CH2CHMe2; Z =
 PhCH2O2C] have been synthesized and evaluated as endothelin converting
 enzyme (ECE) inhibitors. Several of these compds., e.g. I [R =
 MeSO2-L-Lys, MeSO2-L-Lys(Z), R1 = 2-naphthylmethyl, R2 = CH2CHMe2; R =
 MeSO2-L-Lys(Z), R1 = R2 = CH2CHMe2], were potent inhibitors of ECE with a
 high degree of selectivity against neutral endopeptidase (NEP).

IT 180186-02-1P 180186-03-2P 180186-04-3P
 180186-05-4P 180186-28-1P 180186-29-2P
 180186-30-5P 180186-31-6P 180186-32-7P
 180186-33-8P 180321-08-8P 180321-09-9P

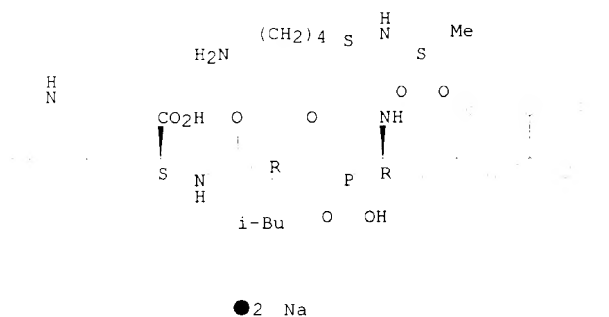
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); SPN (Synthetic preparation); BIOL (Biological
 study); PREP (Preparation)

(prepn. of peptide phosphinylmethylene analogs as highly potent and
 selective endothelin converting enzyme inhibitors)

RN 180186-02-1 HCAPLUS

CN L-Tryptophan, N-[8-(4-aminobutyl)-4-hydroxy-2-(2-methylpropyl)-5-(2-
 naphthalenylmethyl)-4,10,10-trioxido-1,7-dioxo-10-thia-6,9-diaza-4-
 phosphoundec-1-yl]-, disodium salt, [2R-(2R*,5R*,8S*)]- (9CI) (CA INDEX
 NAME)

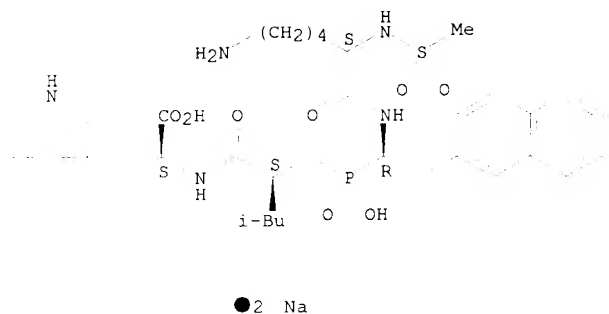
Absolute stereochemistry.



RN 180186-03-2 HCAPLUS

CN L-Tryptophan, N-[8-(4-aminobutyl)-4-hydroxy-2-(2-methylpropyl)-5-(2-naphthalenylmethyl)-4,10,10-trioxido-1,7-dioxo-10-thia-6,9-diaza-4-phosphaundec-1-yl]-, disodium salt, [2S-(2R*,5S*,8R*)]- (9CI) (CA INDEX NAME)

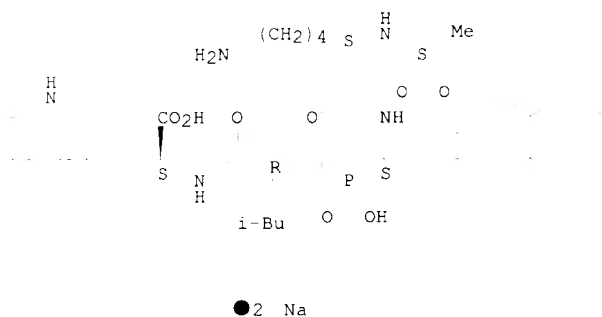
Absolute stereochemistry.



RN 180186-04-3 HCAPLUS

CN L-Tryptophan, N-[8-(4-aminobutyl)-4-hydroxy-2-(2-methylpropyl)-5-(2-naphthalenylmethyl)-4,10,10-trioxido-1,7-dioxo-10-thia-6,9-diaza-4-phosphaundec-1-yl]-, disodium salt, [2R-(2R*,5S*,8S*)]- (9CI) (CA INDEX NAME)

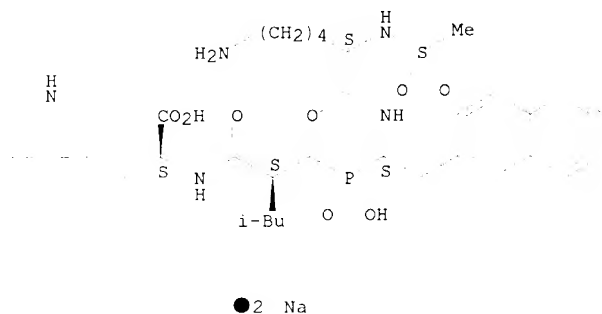
Absolute stereochemistry.



RN 180186-05-4 HCAPLUS

CN L-Tryptophan, N-[8-(4-aminobutyl)-4-hydroxy-2-(2-methylpropyl)-5-(2-naphthalenylmethyl)-4,10,10-trioxido-1,7-dioxo-10-thia-6,9-diaza-4-phosphaundec-1-yl]-, disodium salt, [2S-(2R*,5R*,8R*)]- (9CI) (CA INDEX NAME)

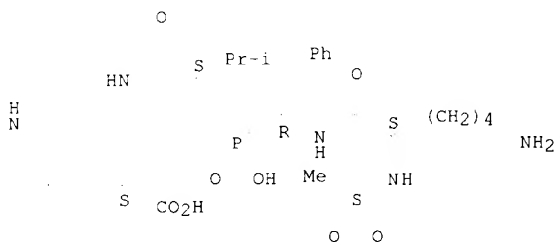
Absolute stereochemistry.



RN 180186-28-1 HCAPLUS

CN L-Tryptophan, N-[8-(4-aminobutyl)-4-hydroxy-2-(1-methylethyl)-4,10,10-trioxido-1,7-dioxo-5-(phenylmethyl)-10-thia-6,9-diaza-4-phosphaundec-1-yl]-, disodium salt, [2S-(2R*,5S*,8R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

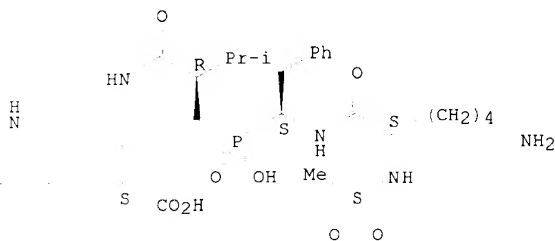


● 2 Na

RN 180186-29-2 HCAPLUS

CN L-Tryptophan, N-[8-(4-aminobutyl)-4-hydroxy-2-(1-methylethyl)-4,10,10-trioxido-1,7-dioxo-5-(phenylmethyl)-10-thia-6,9-diaza-4-phosphaundec-1-yl]-, disodium salt, [2R-(2R*,5S*,8S*)]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

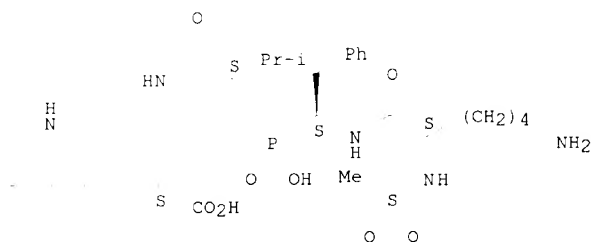


● 2 Na

RN 180186-30-5 HCAPLUS

CN L-Tryptophan, N-[8-(4-aminobutyl)-4-hydroxy-2-(1-methylethyl)-4,10,10-trioxido-1,7-dioxo-5-(phenylmethyl)-10-thia-6,9-diaza-4-phosphaundec-1-yl]-, disodium salt, [2S-(2R*,5R*,8R*)]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

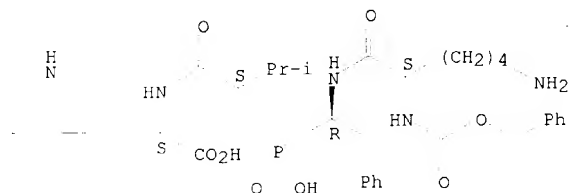


● 2 Na

RN 180186-31-6 HCAPLUS

CN 2,5,11-Triaza-7-phosphatridecanedioic acid, 3-(4-aminobutyl)-7-hydroxy-12-(1H-indol-3-ylmethyl)-9-(1-methylethyl)-4,10-dioxo-6-(phenylmethyl)-, 1-(phenylmethyl) ester, 7-oxide, disodium salt, [3S-(3R*,6S*,9R*,12R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

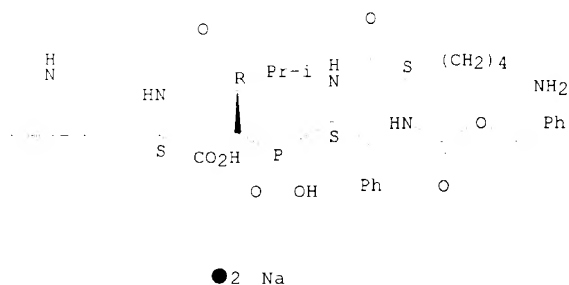


● 2 Na

RN 180186-32-7 HCAPLUS

CN 2,5,11-Triaza-7-phosphatridecanedioic acid, 3-(4-aminobutyl)-7-hydroxy-12-(1H-indol-3-ylmethyl)-9-(1-methylethyl)-4,10-dioxo-6-(phenylmethyl)-, 1-(phenylmethyl) ester, 7-oxide, disodium salt, [3S-(3R*,6R*,9S*,12R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

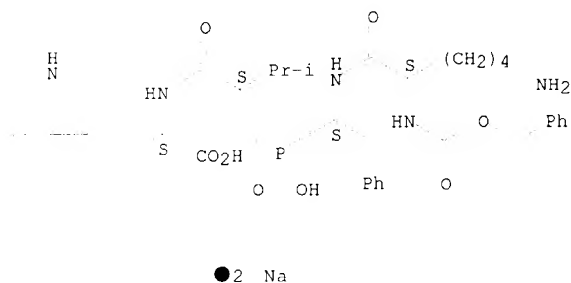


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RN      180186-33-8  HCAPLUS
CN      2,5,11-Triaza-7-phosphatridecanedioic acid, 3-(4-aminobutyl)-7-hydroxy-12-
        (1H-indol-3-ylmethyl)-9-(1-methylethyl)-4,10-dioxo-6-(phenylmethyl)-,
        1-(phenylmethyl) ester, 7-oxide, disodium salt, {3S-(3R*,6R*,9R*,12R*)}-
        [9CI] (CA INDEX NAME)

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Absolute stereochemistry.

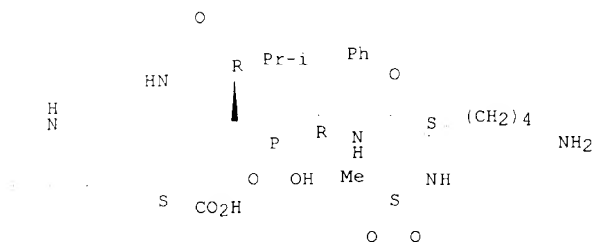


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RN      180321-08-8   HCAPLUS
CN      L-Tryptophan, N-[8-(4-aminobutyl)-4-hydroxy-2-(1-methylethyl)-4,10,10-
        trioxido-1,7-dioxo-5-(phenylmethyl)-10-thia-6,9-diaza-4-phosphaundec-1-yl]-
        , disodium salt, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

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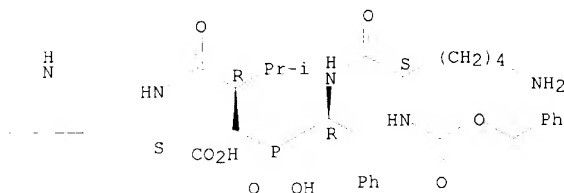
Absolute stereochemistry.



● 2 Na

RN 180321-09-9 HCAPLUS
 CN 2,5,11-Triaza-7-phosphatridecanedioic acid, 3-(4-aminobutyl)-7-hydroxy-12-(1H-indol-3-ylmethyl)-9-(1-methylethyl)-4,10-dioxo-6-(phenylmethyl)-, 1-(phenylmethyl) ester, 7-oxide, disodium salt, [3S-(3R*,6S*,9S*,12R*)]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



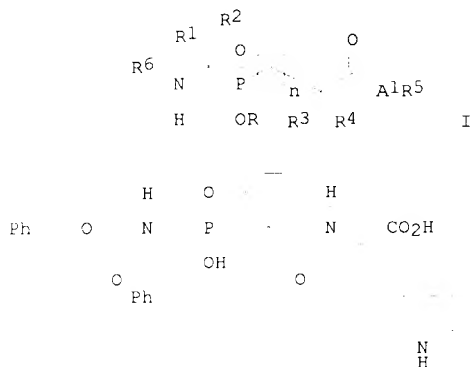
● 2 Na

L6 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1996:50687 HCAPLUS
 DOCUMENT NUMBER: 124:261746
 TITLE: Amino acid phosphinic acid derivatives useful as endothelin converting enzyme inhibitors
 INVENTOR(S): McKittrick, Brian A.; Czarniecki, Michael F.; Chackalamannil, Samuel; Chung, Shin; Defrees, Shawn; Stamford, Andrew W.
 PATENT ASSIGNEE(S): Schering Corp., USA
 SOURCE: U.S., 34 pp.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5476847	A	19951219	US 1994-267630	19940629
CA 2191454	AA	19960111	CA 1995-2191454	19950619
WC 9600732	A1	19960111	WO 1995-US7128	19950619
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, UZ, VN				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9529013	A1	19960125	AU 1995-29013	19950619
EP 767794	A1	19970416	EP 1995-924573	19950619
EP 767794	B1	20000202		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 10502081	T2	19980224	JP 1995-503179	19950619
AT 189455	E	20000215	AT 1995-924573	19950619
ES 2144131	T3	20000601	ES 1995-924573	19950619
PRIORITY APPLN. INFO.:			US 1994-267630	A 19940629
			WO 1995-US7128	W 19950619

OTHER SOURCE(S): MARPAT 124:261746

GI



AB Phosphinic acid derivs. I or a pharmaceutically acceptable salt thereof, wherein R is H, alkyl or alkanocyloxymethylene; R1, R2, R3 and R4 are H, alkyl, alkenyl, alkenylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxyalkyl, carboxyalkyl, thioalkyl, alkoxythioalkyl, aminoalkyl, alkylaminoalkyl, cycloalkyl-substituted alkyl or heterocycloalkyl; or R1 and R2 form a cycloalkyl ring of 3-8 members and R3 and R4 are as defined; or R3 and R4 form a cycloalkyl ring of 3-7 members and R1 and R2 are as defined; or R1 and R2 together, and R3 and R4 together, each form a cycloalkyl ring; R5 is OR9 or NHR9, wherein R9 is hydrogen or alkyl; n is 0 or 1; Al is p-aminobenzoyl or p-aminobenzenesulfonyl, or Al and R5 together form a radical of an

.alpha.-aminoacyl deriv.; and R6 is phenylmethoxycarbonyl, arylcarbonyl, heteroarylcarbonyl or A2R7, wherein A2 is a divalent .alpha.-aminoacyl radical, and R7 is a substituent on the .alpha.-amino atom selected from H, R8OCO, R8SO2 and R8NHCO, wherein R8 is aryl, arylmethyl or (C1-C8) alkyl; are disclosed for use as endothelin converting enzyme inhibitors; also disclosed are a genus of novel compds. wherein R3 and R4 form a cycloalkyl ring. Thus, e.g., Me ester II (prepn. given) was sapond. to the carboxylic acid which exhibited endothelin converting enzyme inhibiting activity of IC50 = 190 nM. Pharmaceutical formulations were given.

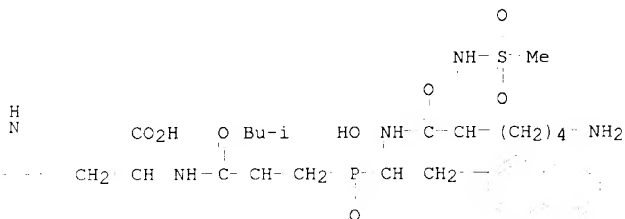
IT 174768-21-9P 174768-27-5P 174768-34-4P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(amino acid phosphinic acid derivs. useful as endothelin converting enzyme inhibitors)

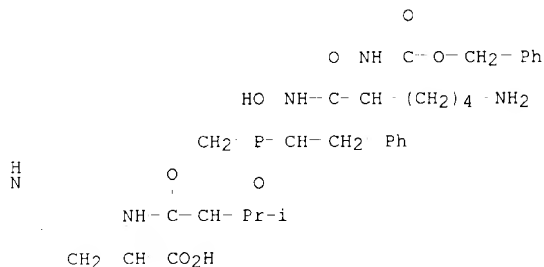
RN 174768-21-9 HCAPLUS

CN L-Tryptophan, N-[6-(4-aminobutyl)-4-hydroxy-2-(2-methylpropyl)-5-(2-naphthalenylmethyl)-4,10,10-trioxido-1,7-dioxo-10-thia-6,9-diaza-4-phosphaundec-1-yl]- (9CI) (CA INDEX NAME)



RN 174768-27-5 HCAPLUS

CN 2,5,11-Triaza-7-phosphatridecanedioic acid, 3-(4-aminobutyl)-7-hydroxy-12-(1H-indol-3-ylmethyl)-9-(1-methylethyl)-4,10-dioxo-6-(phenylmethyl)-, 1-(phenylmethyl) ester, 7-oxide (9CI) (CA INDEX NAME)



RN 174768-34-4 HCAPLUS

CN L-Tryptophan, N-[8-(4-aminobutyl)-4-hydroxy-2-(1-methylethyl)-4,10,10-

trioxido-1,7-dioxo-5-(phenylmethyl)-10-thia-6,9-diaza-4-phosphaundec-1-yl]-
(9CI) (CA INDEX NAME)

